The Role of Biotechnology and Bioinformatics in FDA's Critical Path Initiative

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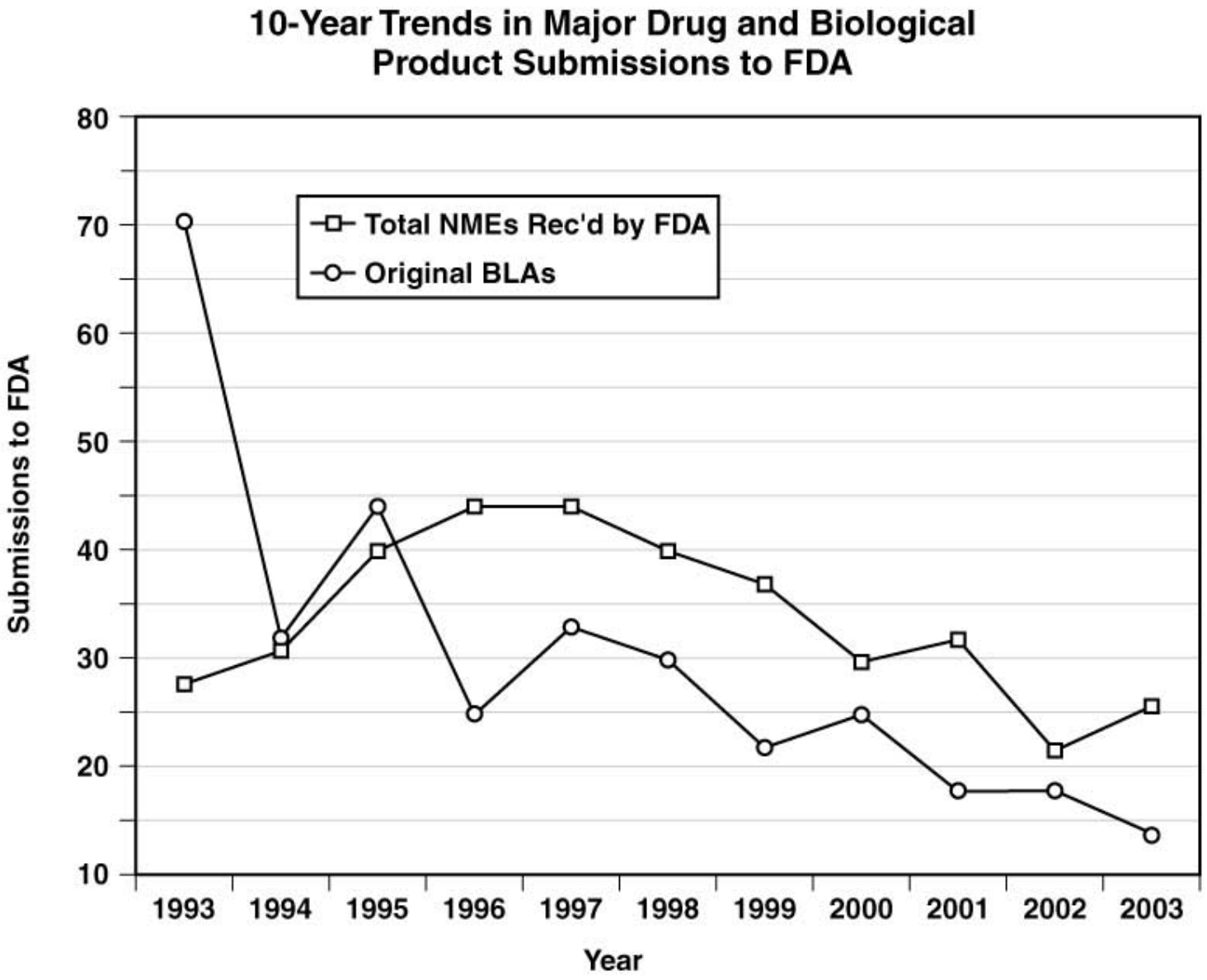
Thesis of FDA's Critical Path Initiative

- The drug and device development processes need to be modernized
- The clinical use of these medical products needs to be improved
- The healthcare system suffers from serious problems, many related to product use
- New scientific advances, especially in biotechnology and bioinformatics, have the potential to address these issues, but must be applied specifically to the problems

The Drug Development Process Needs Improvement

- Current development very challenging
- Pipeline problems persist
- Post phase 1 failure rate increasing
- Drug safety issues lead to calls for larger and longer premarket trials
- Productivity in crisis: ever-increasing investment and decreasing output


10-Year Trends in Major Drug and Biological Product Submissions to FDA
Total NMEs Rec'd by FDA
Original BLAs
Submissions to FDA
80
70
60
50
40
30
20
10
1993
1994
1995
1996
1997
1998
1999
2000
2001
2002
2003
Year

Ten Year Trends Worldwide

- 2004 marked a 20-year low in introduction of new medical therapies into worldwide markets
- DiMasi, et al. (2003) estimated that the capitalized cost for self-originated NMEs developed by multinational pharma & approved in 2001 would be about $1.1 B per NME.
- Disincentive for investment in less common diseases or risky, innovative approaches

Issues in Healthcare

- US healthcare costs becoming politically? or societally? unsustainable (e.g., debate about drug importation)
- With Medicare Part D federal government becoming highly involved with payment for medications
- One result: demand for more “value” i.e., greater certainty, about outcomes of therapy
- Increasing pressure for comparative studies, long term outcome trials, etc, premarket

These Trends are Not Sustainable

- Rising costs of development, coupled with continuing high clinical failure rate are on a collision course with societal demand for more certainty prior to product approval
- Despite these problems, unmet medical needs persist and never has there been more scientific opportunity for addressing them
- A new development model or paradigm is needed

FDA's Critical Path Initiative

- Launched in 2004 with "Innovation/Stagnation" white paper
- Calls for rapid incorporation of new science into medical product development pathways to improve informativeness of process as well as predictability
- 2006 Report and List: 76 scientific projects as examples of needed approach

First Achievement of Critical Path: Defining (Naming) the Problem

- Most non-technical stakeholders (Congress, medical community, etc) did not grasp this issue
- FDA often blamed for development problems—undiscovered safety issues as well as slowdowns of important drugs and devices
- Agency generally not funded for applied science to improve development
  - Biologics and device programs have (very modest) research funds
  - Drugs program does not have any significant funding

Reaching Agreement on Addressing the Problem

- Stakeholders such as patient advocacy groups, medical professional societies, and some academics rapidly on board
- Industrial representatives agreed with problem definition but not sure of its relative importance
- Slow buy-in by FDA staff (generally group-by-group as projects in their regulatory area are addressed)
- Consensus reached over time
  - IMI in Europe

If We Agree on Problem: Where Will Funding Come From?

- Critical Path proposed collaborative ways of accomplishing objectives
- Funds are scarce—so pool resources, especially those that have been underutilized
- Use industry data generated for compound development for additional purposes
- Use NIH-funded trials and research to help qualify promising biomarkers
- Utilize industry trials for additional purposes

Major Opportunities for Modernization per March 06 Report

- Biomarker Qualification
  - In-vitro diagnostics
  - Imaging
  - Preclinical toxicogenomics
- Clinical Trial Modernization
- Bioinformatics
- Modernizing Manufacturing
- Pediatric Treatments
- Public Health Emergencies

How Do These Topics Fit With Subjects of this Workshop?

- New biomarkers will be the results of biotechnology
  - Genomic, proteomic, metabolomic and other molecular in vitro assays
  - Molecular and functional imaging in vivo
- Bioinformatics will be the means to connect biomarker information with clinical trial data and surveillance data to provide the clinical meaning
- Many new therapeutic products will result from biotechnology

Critical Path Initiative Progress Since 2004: Selected Areas

- Biomarker Development
- Bioinformatics

Biomarker Development

- Framework for adoption and regulatory use
- International progress
- Pharmacogenomics
- Safety biomarkers
- Cancer
- Targeted therapy
- Imaging

Biomarker “Qualification”

- Previous concept of biomarker “validation” had slowed field
- Few biomarkers developed to the point of regulatory usefulness
- Developed concept of “qualification”= fitness for use: a contextual definition
- Realization that different levels of evidence appropriate for different uses

Conceptual Framework for Biomarker Qualification and Regulatory Acceptance: Progress

- Broad acceptance of notion of “qualification” or “fitness for use”
- Regular meetings between CDRH and CDER on use of diagnostics with drugs
- Formal biomarker qualification process set up at CDER
- Agency-wide biomarker qualification process being developed

Biomarker Framework

- FDA concept paper on topic due before the end of this calendar year
- Agency review divisions being surveyed on their use of and terminology for biomarkers (highly variable)
- FDA evaluating a qualification package and more are expected
- Dissemination methods under discussion

International Progress on Biomarkers

- Biomarker discovery and development a major theme of EU's "Innovative Medicine Initiative" (IMI)—proposed funding 1B Euros over 2007-13 from EU, with matching contributions from industry
- EMEA and Japanese regulators participating in FDA biomarker qualification process
- Step 2 guidance at ICH on pharmacogenomics terminology (E15)

Biomarker Collaborative Efforts

- The Biomarker Consortium": Foundation for NIH FDA/NIH/PhRMA/BIO and many other partners
- MACQ Consortium: FDA/NIST/NIH and many others
- C-Path Institute, Tucson, AZ: Critical Path effforts
- Duke University/FDA: cardiac safety

Pharmacogenomics

- FDA instituted “voluntary genomic data submission” process in 2006
- Safe harbor approach for discussing genomic findings with regulators
- Multiple submission and extensive information exchange since then
- Expansion to vXDS: voluntary eXploratory data submission

Pharmacogenomic Biomarkers

- Announced relabeling: 6MP, irinotican, warfarin, codeine...more to come
- Policy arena: ASR guidance, draft IVDMIA guidance causing a great deal of controversy
- “Pharmacogenomic Data Submissions: Companion Guidance” issued 8/07

Safety Biomarkers

- Side effects don't happen to everyone: so what causes a specific individual to have one?
- Need to improve drug safety through better *mechanistic* understanding of AEs
- Certain biomarkers may be low hanging fruit in improving drug safety
- Opportunities: pharmacogenomics; genetic basis of AE's, cardiac repolarization, new empirical safety biomarkers

Safety Biomarkers: What are the Obstacles to Progress?

- Another area where “no one has been in charge”
- Much academic research in this area
- Real world always more complex and requires much more study
- Consortia presented today are taking first steps, will need worldwide cooperation to achieve robust clinical qualification
- Need links with informatics-based safety surveillance and datamining

Biomarkers in Cancer

- FDA has robust partnership with NCI (IOTF)
- OBQI= Oncology Biomarker Qualification Initiative: FDA/NCI/CMS
- Cancer steering committee of “The Biomarker Consortium”
- AACR/FDA/NCI project on technical aspects of biomarker development
- ASCO/FDA/NCI project on clinical trials using markers (e.g., adaptive trials)

Biomarkers and Targeted Therapy: Progress

- Project with C-Path Institute/NCI
- FDA plans to issue Drug-Diagnostic co-development guidance this fall
- Need acceptance of trial strategies that allow for study of dx and drug performance within same development program: particularly various types of adaptive designs; these are being explored
- Beginning to see development plans including biomarkers for enrichment/targeting

Imaging Biomarkers

- Great promise—slow progress
- Need to enhance agency review function
- Alzheimer's Neuroimaging Initiative one effort to study natural history along with imaging biomarkers
- Need way to support general human research use of molecular probes
  - Without repeating preclinical workup
  - With due respect to IP

Biomarkers: Overall Issues

- Pharmaceutical industry experiencing financial concerns—some reluctance to embark on collaborative projects
- Other funding sources for biomarker qualification remain tenuous; NIH in general more focused on basic research
- Clinical skepticism remains: confusion with surrogate endpoint problems??
- Insurers undervalue diagnostics: lack of viable business model for IVDs a problem; payers want outcomes data for new markers

Critical Path Efforts in Bioinformatics

- Quantitative disease modeling and simulation
- FDA's internal informatics systems
- The future for medical product surveillance

Modeling and Simulation

- FDA has created several quantitative disease models and presented analyses during Phase 2 meetings
- Such models capture clinical natural history along with known biomarkers and effects of interventions
- Clinical trial data on specific agent can be incorporated: ie, PK/PD
- Conduct simulations of efficacy trials

Bioinformatics: FDA Systems

- Bioinformatics Board Structure set up at FDA supported by Critical Path Programs, Office of the CIO, and Office of Planning
- Goal: Agency wide systems
- Five Business Review Boards (BRBs), to set business needs for specific cross-agency business processes

Bioinformatics

- Data standards council also supported by CP
  - Relevant data standards to HL-7
  - Structured product label standards
- Pertinent BRBs:
  - Premarket: electronic submission, tracking and review processes
  - Postmarket: electronic adverse event reporting and database management
  - Quality: manufacturing regulation and tracking inspections, product movement
  - Scientific computing/computational science: needs of laboratories and quantitative scientists

Bioinformatics: Future

- Why focus on these agency-wide systems? Part of “information supply chain”
- FDA needs a systematic method of knowledge management in order to regulate efficiently
- Supported by agency reviewers and scientists
- Efficient transfer of regulated product information across various sectors
- Create a structure that can link findings in the health care system to what is known scientifically
- Open the door for datamining and other techniques

What's Next for Critical Path?

- Depends in part on funding
  - Government FY begins 10/1
  - FDA may not have an appropriation then
  - PDUFA renewal still before Congress
  - Congress discussing establishment of FDA foundation to support Critical Path research
- External collaborations robust and will grow
- Centers poised to aggressively take up new projects if resources available

Areas of Focus in ‘08

- Quantitative disease models
- Drug-Diagnostic co-development
- Nanotechnology
- Clinical trial modernization
- Numerous indication-specific projects
  - Pain
  - Cancer
  - Rheumatic diseases

Quantitative Disease Models

- Good early progress at FDA
- In my opinion, this is part of the future of drug development
- Basis for systematizing biomarker information linked to clinical course; simulations of interventions
- Needs infusion of resources at FDA

Drug-Diagnostic Co-Development

- Issuance of guidance: policy and scientific development
- Procedurally, will require close CDER and CDRH collaboration
- Methodologic approaches to development program will keep advancing
- Hope to see more actual cases: linking up drug therapy with biotechnological information and bioinformatics

What is the Vision for Drug Development of the Future?

- Preclinical toxicology and clinical development move from empirical evaluations to quantitative model-based learn-confirm cycles
- Necessary degree of confirmation pre-market dependent on indication (as is the case currently)
- Predictive capacity of development system greatly enhanced
- Amount of information generated by system greatly increased

What is the Vision for Drug Development of the Future?

- Finally: We (collectively, collaboratively) will build a postmarket evaluation system based on the emerging EHR that will provide robust data on the real-world outcomes of the use of drug products, and will be linked to the preclinical and clinical development data: the ultimate in bioinformatics